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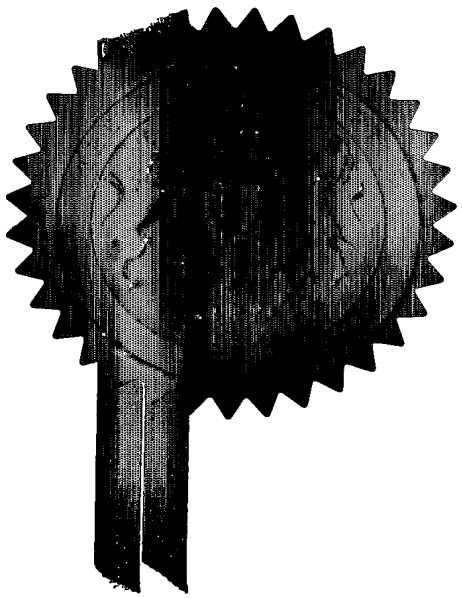

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Request for grant of a patent

The Patent Office
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1. Your reference
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2. Patent Application Number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if known)*

If the applicant is a corporate body, give the country/state of its incorporation
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State:

4. Title of the invention

Anaesthesia Monitor

5. Name of agent
"Address for Service" in the United Kingdom to which all correspondence should be sent
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London WC1V 6BX

Patents ADP number
1826001

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BERESFORD & Co

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Patent disclosure

Anaesthesia monitor

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Introduction

General anaesthesia is a very common medical procedure. Despite its wide usage, it is still a high-risk treatment. The level of effectiveness and the metabolic clearance of an anaesthetic varies widely from patient to patient. In order to optimise patient care, minimise side effects and recovery time and maximise the anaesthetic effectiveness, close monitoring of the level of the anaesthetic in the patient's body is required. One particular effective way to achieve this aim is to monitor the concentration of anaesthetics in biological fluids.

One very popular and highly effective anaesthetic is propofol. It has a profile that allows it to be used in a number of procedures. Patient recovery is quick and without significant side effects. The performance of propofol is characterised by fast distribution into the tissues and rapid metabolic clearance. These properties account for propofol's rapid onset and short duration of action; mean induction time is 30 to 40 seconds after injection. Clinically, maintenance of adequate sedation requires a constant infusion of propofol. Discontinuation of propofol infusion results in a rapid decrease in plasma concentrations and prompt awakening. Therefore, close control of propofol concentration is highly advantageous for appropriate and effective anaesthesia.

At the current time, dosage of propofol is determined and regulated by controlling the rate of infusion, for example, by using a syringe pump. One example is a software-driven syringe pump, called the Diprifusor™. This device dispenses propofol based on the initial input of the patient's data, such as weight and gender, and therefore assists in the control of delivery. As the method is based on average response of the patient to the drug, it has significant shortcomings with normal function giving dosage errors of ~25%.

At present, analysis of propofol concentrations is laboratory-based and takes from hours to days in order to get a result. This analysis may be useful for some academic purposes, but is not relevant for controlling the propofol administration. More recently, a research group at the Horticulture and Food Research Institute of New Zealand Limited has developed synthetic polymers for binding of phenols, in particular propofol. These polymers are prepared as particles for use in extraction columns and as membranes for use in single-use sensors or large-scale analysers, employing metal or

carbon electrodes or optical fibre based detection principles. These methods require a separate blood sample to be taken from the patient and transported to the analyser for each analysis undertaken. This introduces significant time delays, handling issues etc. Frequent sampling of blood, as required for continuous control of the anaesthesia level, will result in significant blood loss by the patient, which would be detrimental to the patient's health.

In order to control and optimise the delivery of anaesthetics, such as propofol, clinicians and anaesthesiologists require a monitoring device which will monitor the level of anaethetics and/or their derivatives in biological fluids in near real time without any significant side effects for the patient.

The invention

The invention disclosed in this document is a monitoring device which will monitor the level of anaesthetics and/or their derivatives in biological samples, such as blood, serum, plasma, interstitial fluids, saliva, cerebrospinal fluid, breath or other fluids, which may be optionally purified to remove, for example, red blood cells, platelets etc. The measurement approaches described are applicable to humans and animals (in the following being referred to as "the patient"). Methods of manufacturing or operating the device are also disclosed.

In one embodiment the device consists of a sensor element which is functionalised with a chemical recognition element which preferentially reacts with or binds one or more anaesthetic(s) being administered to the patient and/or their derivative(s) (the "analyte(s) of interest"), for example, but are not limited to, intravenously administered anaesthetics, such as propofol. The chemical recognition element may be a biologically derived substance, such as an enzyme, antibody, protein, micro-organism, cell, bacterium or virus to name but a few, or an artificial or synthetic receptor, such as a molecularly imprinted polymer (MIP). The latter are particularly attractive in the context of this invention as they have advantages with respect to biologically derived receptors in terms of robustness and cost and also difficulties associated with raising a suitable biologically derived receptor.

The sensor may also operate in a competitive mode. In this mode of operation, the chemical recognition element(s) which respond(s) to one or more other substances which are displaced from the recognition element by the analyte(s) of interest, but not directly to the analyte(s) of interest. In this case, the sensor signal will decrease in the presence of the analyte(s) of interest as the substance(s) are displaced from the recogntion element(s). In one particular embodiment, semi-permeable membranes and/or other confinement structures may be used to trap the substance(s) close to the sensing elements. In another embodiment, the substance(s) may react with the analyte(s) of interest.

In another embodiment, the chemical recognition element(s) respond(s) to the analyte(s) of interest by releasing a substance which is detected by the sensing element, either directly or indirectly. In a further example of the invention, the recogntion element may provide a form of chemical amplification, e.g. release two molecules of the substance for every molecule of the analyte(s) of interest. The

substance released may also be used to provide other benefits, e.g. it may be a form of medication beneficial to the patient.

The sensor can use a wide range of transduction or sensing principles to detect the interaction of the chemical recognition element with the analyte(s) of interest. Transduction principles include, but are not limited to, amperometric, conductimetric, potentiometric (in particular, ion-sensitive field effect transistor, ISFET, or chemically modified field effect transistor, CHEMFET, or more generally any device where the input is a chemical reaction or the presence of a particular chemical in close proximity to the field effect device), gravimetric, thermal, optical, resonant or surface-acoustic wave detection.

The sensor may be combined with a sampling device which will enable the sampling of the respective fluid from the patient being treated. Of particular interest are patient-connected sampling systems, for example, an arterial or venous lines, which enable the sampling of blood from the patient. Alternatively, the sensor may be associated with a bypass system, e.g. a bypass used in cardiac surgery.

Blood may be withdrawn once, repeatedly or periodically over the sensor or into a container (e.g. connected to the sensor or for transport to the sensor) in order to enable the analysis. After the analysis the blood may be returned to the patient or discharged, e.g. to waste. Other sampling methods include syringes, intra-cranial drains (e.g. for the analysis of cerebrospinal fluid), microdialysis probes or microneedles (e.g. to access interstitial fluids and/or blood). Others are known to those skilled in the art.

The sensor may be configured to analyse samples from the patient repeatedly or periodically. Alternatively, it may be a configured to be used once, e.g. as a disposable or test strip. In another embodiment, the sensor is incorporated into a larger instrument, for example, an in-vitro analyser, configured to be used once or a number of times. The sensor may also be operated in a mode where it is flushed with a suitable solution or mixture after each use, for example, to clean the sensor, to remove substances contained in the sample from the sensor or to enable samples to be analysed repeatedly.

Furthermore, the sensor may be used continuously. In this case, the affinity of the chemical recognition element can be adjusted to facilitate the operation of the sensor in this mode.

The analysis can be conducted on-line, which is of particular advantage for the control of anaesthesia delivery. Alternatively, other embodiments of the invention may also be employed for off-line analysis.

The chemical recognition elements may be associated with the sensing elements in a variety of forms. They can be thin layers, in particular mono- or multilayers, of receptors or recognition elements deposited on the sensing elements. Alternatively, they may be membranes which respond to the presence of the analyte(s) or react with the analyte(s) in a known manner. Alternatively, membranes can act as filters which allow the analyte(s) to pass, while restricting the passage of other substance

interfering with the measurement. The recognition elements may also take the form of particles contained within or confined below a membrane. Other forms are known to those skilled in the art of preparing and using these receptor materials.

Furthermore, the chemical recognition elements may react with the analyte(s) of interest to release another substance or generate an event which is detected by the sensor element.

In some cases, further purification and concentration of the analyte(s) of interest can be achieved *in situ* by encapsulating or covering the sensing elements in one or more material(s), solid or liquid, into which the analyte(s) of interest preferentially partition(s) over the test medium it is in. One particular example, is an analyte which is in a polar test medium, but which partitions preferentially into a non-polar solvent. A membrane may be used to enclose the partitioning material, if required. An illustration of one particular embodiment of this invention using this approach is shown in Figure 1.

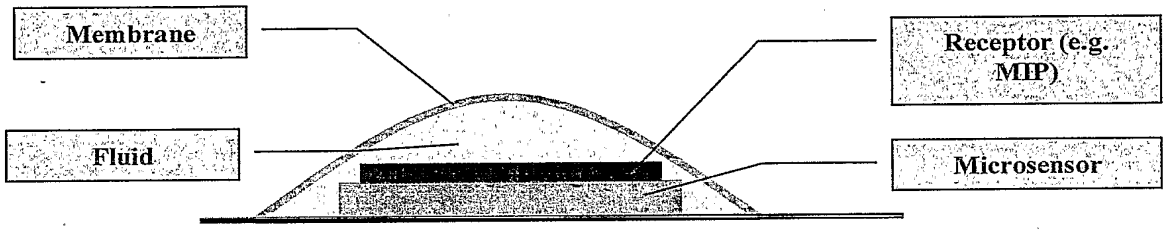

Figure 1: Schematic illustration of one particular embodiment of the invention.

One particular embodiment of the invention employs micromachined sensing elements to detect the analyte(s) of interest. Micromachined sensors are particularly attractive as they are of low cost and small size and, hence, can be used close to the patient, avoiding transport of the sample to be analysed from the patient to the analyser.

A further embodiment of our invention employs a silicon-based microsensor chip which incorporates one or more chemical sensing elements. A particular example of a multiple-analyte sensor is shown in Figure 2.

This particular chip employs potentiometric, in particular ISFETs and CHEMFETs, amperometric and conductimetric devices functionalised to respond to the analytes of interest. However, the invention is not limited to multi-parametric micromachined chemical sensors and can employ a wide range of other microscopic and macroscopic sensors and transduction or sensing principles (see above).

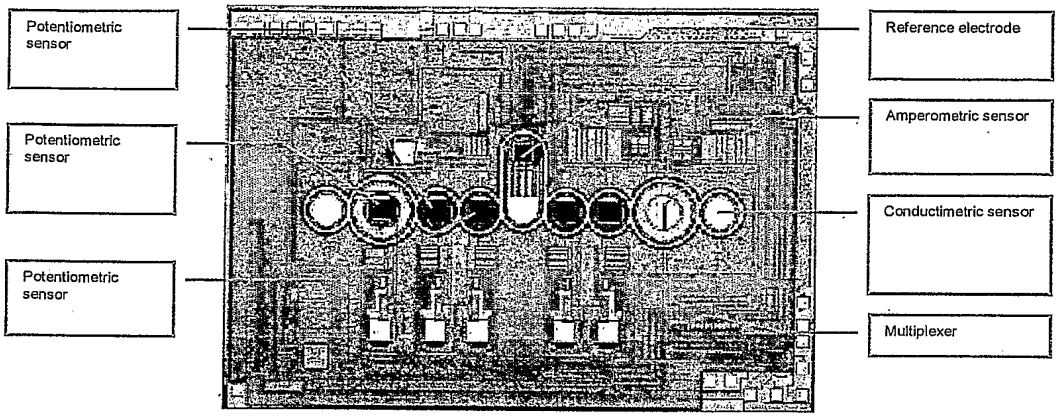

Figure 2: Example of a multi-parameter chemical sensor chip developed by Sphere Medical Ltd.

The sensing elements may be functionalised to detect the analyte(s) of interest in a wide variety of ways, including, but not limited to deposition, evaporation, spin-coating, printing, ink-jet printing, dropping, spotting, centrifugation, screen printing, dripping, pipetting, droplet transfer (using e.g. a needle structure) etc. of suitable recognition elements or a mixture containing reagents which will lead to the creation of these elements.

In addition to the approaches outlined above, a further method by which to functionalise the sensing element(s) on such a single- or multi-parametric chip is by the use of confinement structures on the device substrate around one or more features, e.g. sensor element(s). The structures may be circular or of any general shape which will be suited to the application in hand. They can be created during or following the manufacturing process of the device and can be made from a variety of materials, such as polymers, photoresists (e.g. polyimide or SU8), passivation materials (e.g. silicon oxide, nitride or oxynitride), metals, insulators or semiconductors. In general, the shape of the structures will be chosen to suit the size and shape of the transducers. These structures would act to contain the mixture of some or all of the reagents that will be used to create the chemical recognition element, e.g. the synthetic receptor(s), the partitioning material and/or membrane of the device or sensor. Due to the containment within the structure a larger number of functionalised sensor elements can be created in a given surface area on the substrate. Moreover, different mixtures can coexist on the surface of the substrate at the same time without mixing or cross-contamination. In addition, the confinement structures provide a means of achieving a uniform or complete coverage of the feature or sensor element even if parts of the mixture (e.g. a solvent) evaporate.

The confinement structure(s) may also provide means to improve the adhesion of the chemical recognition element on the substrate, sensor element or confinement structure, for example, by mechanical keying or the formation of chemical bonds.

Single and multiple dispensing heads may be used in order to enable serial or parallel deposition into the confinement structures. An example of such a deposition process is shown in Figure 3.

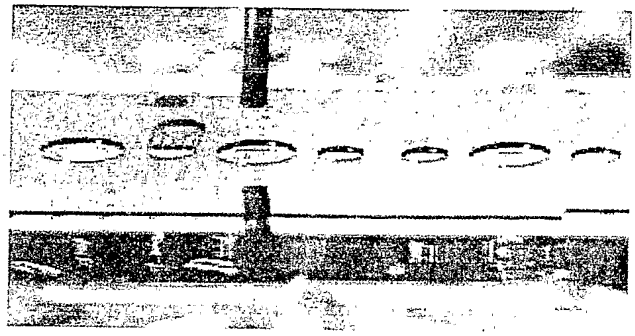

Figure 3: Deposition of materials into confinement structures around sensor elements on the chip shown in Figure 2 using a microspotter.

The confinement structures may also be used to aid the deposition of other material(s), for example electrolytes and the partitioning material(s), associated with the sensing element(s) for the analyte(s) of interest. An illustrative example of this embodiment is shown in Figure 4. Different confinement structures may contain different materials, e.g. partitioning materials. It is therefore possible to create different environments, e.g. polar and non-polar, on the same substrate.

One example where this approach may be advantageous is the detection of substances which exist as emulsions in solvents. Examples include propofol products in the form of emulsions.

In addition to providing preferential partitioning of analyte(s) into structures and materials associated with particular sensing elements, this approach may also provide a specific or desirable environment around a sensing element or receptor, e.g. to improve its performance. For example, many MIPs have been designed or optimised for operation in non-polar media. By providing a localised non-polar environment on the substrate around the receptor, these MIPs may be employed in a chemical sensor operating in polar solvents for analytes which will partition into the non-polar material.

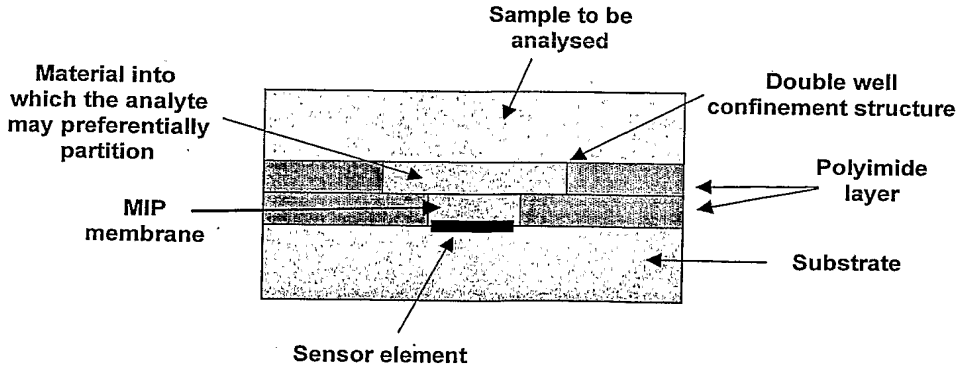

Figure 4: Schematic representation of an example of one embodiment of the invention where the sensing element is functionalised with a MIP and a material is deposited on top of a sensor element into which the analyte(s) of interest preferentially partitions.

In order to eliminate spurious effects associated, for example, with temperature fluctuations, it is generally advantageous to combine two identical transducer devices or sensing elements, only one of which is sensitive tot he analyte(s) of interest, and to carry out differential measurements. The differences in the response of the two is therefore derived from the analyte(s) of interest; other interfering effects are fully or largely compensated for.

Using the present invention, an additional advantage may be obtained by carrying out a differential measurement on two transducers or sensing elements that are identical except for the fact that one is coated with a molecularly imprinted material and the other is coated with a material of identical composition, polymerised and/or crosslinked in the absence of the template molecule (see Figure 5 for a schematic illustration of one particular embodiment of this aspect of the invention). The reason for this is that a MIP material can have, besides the binding sites specifically suited to the analyte(s) to be detected, non-specific sites which can bind other molecules. On the other hand, the material polymerised in the absence of the template possesses only non-specific sites. It is thus possible to compensate either fully or partially for the interference which may be due to molecules other than the analyte(s), which become bound to the sensitive layer by non-specific interactions. In the present invention, the two transducers can be combined on the same substrate by creating confinement structures around the individual sensor elements and realising the template-imprinted MIP and the material crosslinked in the absence of a template in the confinement structures around the two respective sensing elements.

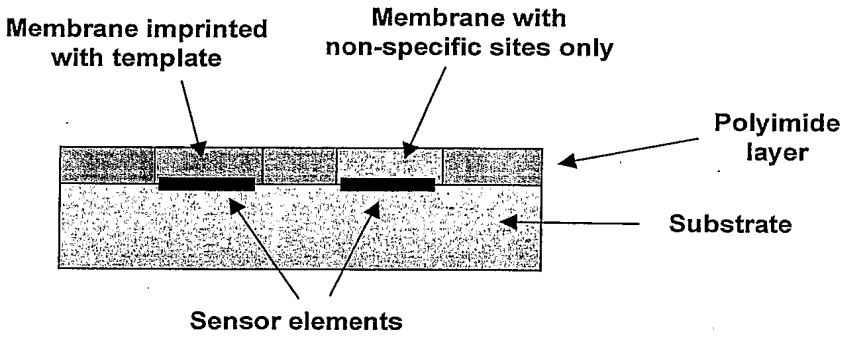

Figure 5: Example of a substrate with two identical sensing elements, one of which is functionalised using a MIP imprinted with the analyte(s) of interest, while the other is functionalised with a membrane of identical composition, but polymerised in absence of the template. This second sensing element serves as a reference sensor to identify and account for non-specific interactions of the analyte(s) and test medium with the MIP.

Rather than providing a reference transducer with a receptor material which is crosslinked in the absence of a template molecule, further embodiments of the invention employ one or more reference sensor(s) functionalised with a receptor material sensitive to any of the following species or any combination thereof:

- One or more interfering species to the analyte(s) of interest;
- One or more products of chemical reactions involving the analyte(s) of interest, e.g. a metabolite;
- Derivatives of the analyte(s) of interest;
- Any other chemical species which may affect the sensor operation.

Other reference sensors may be created from sensing elements without partitioning material or with different partitioning material. Yet another approach involves the creation of a reference structure by the functionalisation of a sensing element with a MIP which is pre-loaded with the analyte(s) of interest or a derivative, i.e. only has non-specific site available for binding.

In the simplest embodiment, the signal from the reference sensor may be subtracted from that of the sensor element which is functionalised to the analyte(s) of interest. However, more elaborate compensation schemes may be employed, known to those skilled in the art.

The device may also contain means for temperature measurement and temperature control. For example to enable measurements to be carried out at a certain temperature or to change the temperature.

In addition to measuring only one or more anaesthetic substances, the sensor may be configured to measure a wider range of substances, for example, other drugs, disease markers or blood parameters (such as dissolved gases, pH, electrolytes). Multi-parameter measurements of this type may be accomplished using a micromachined sensor chip, for example, a chip as shown in Figure 2.

In many cases, patients are sedated while being artificially ventilated. It is therefore of particular advantage to combine anaesthesia monitoring with the measurement of parameters required to control the operation of the ventilator (e.g. pO_2, pCO_2, pH) in one measurement system.

More generally, the invention also comprises measurement systems which monitor the level of anaesthetics in a patient together with other parameter which characterise the health of a patient, monitor particular markers indicating disease states or direct the patient's treatment.

By simultaneously measuring concentrations of the analyte(s) of interest in other tissues, fluids or body compartments it is possible to determine the kinetic profile of analytes within the body. Potentially, an extremely useful approach would be to measure either separately or simultaneously related metabolites of the analyte(s) of interest to give information on the physiological passage/pharmacokinetics of the analyte(s).

Information derived from such a sensing system could be used to provide the input to an expert system to guide the anaesthetists or enable closed-loop drug administration when coupled with the appropriate administration device and control algorithm.

Another embodiment is shown schematically in Figure 6. It consists of a measurement system which provides on-line and on-demand measurement of the level of anaesthetics and/or other parameters in the patient's blood. It comprises a disposable sensor, for example, a packaged analysis chip, as shown in Figure 2, functionalised for the detection of the analyte(s) of interest and other parameters, which is integrated into or connected to a vascular access device, e.g. a cannula. Depending on the application the sensor may be connected to an artery, vein or other sampling site of the patient. Alternatively, it may be integrated or connected to an existing monitoring system attached to the patient, for example, but not limited to, an invasive blood pressure monitoring system, as shown in Figure 6. The sensor may be connected to an electronics unit which will analyse the signals and compute the desired output. The output may be displayed on a local display associated with the electronics. The electronics unit may also be connected to the bedside vital-signs monitor in order to provide connectivity to the hospital information system for display, trending, data storage, data analysis and access to the electronic patient records.

The electronics or parts thereof may be integrated into the sensor package or form a separate unit.

Whenever required, blood is sampled from the patient and flushed over the sensor. Once the sample is analysed, the blood may be flushed back into the patient or to waste. After the sample is analysed, a suitable solution may be flushed across the sensor, e.g. to clean the sensor and/or remove substances contained in the sample from the sensor.

Sampling can occur manually, for example using a syringe connected to the sampling port shown in Figure 6 to withdraw blood from the patient, or automatically, using, for example, a pump or syringe pump connected to the line.

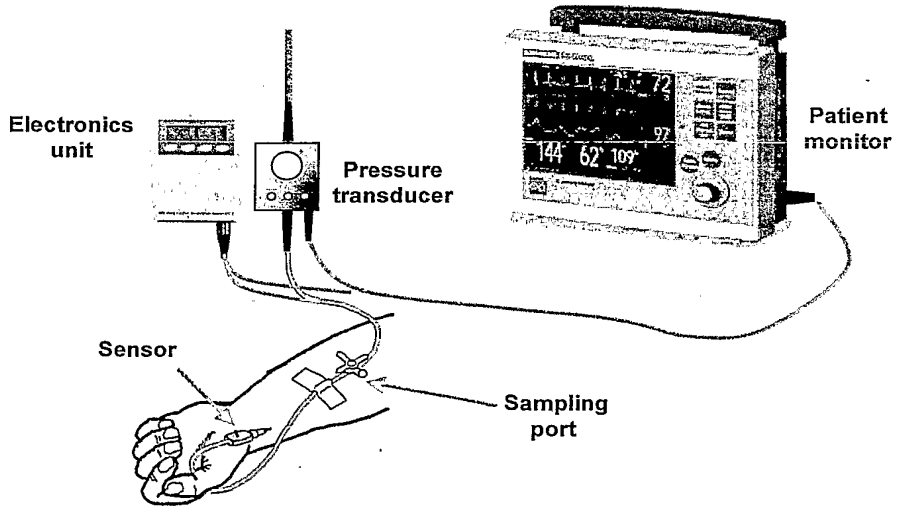

Figure 6: Illustration of a monitoring system attached to a vascular access line.

The benefits of this system over existing solutions are: improved patient care, reduced blood contact and infection risk to patient and caregiver, reduced blood withdrawal from the patient, and reduced cost.

The sensor can be a disposable device which is used once, repeatedly or periodically. Of particular advantage is the use of a per-patient disposable sensor which is used repeatedly over a period of time, for example, minutes, hours, days, weeks or longer, or the while the patient is sedated or within a hospital or care environment. The menu of sensors on the chip will be configured for specific applications.

Also, MIP materials represent only one class of recognition element which can be used in conjunction with the invention. In this document, MIP are used for the purpose of illustration. Other materials, in particular other biologically derived or synthetic receptors, may be employed instead of or in addition to MIP.